

# Ganetespiib limits ciliation and cystogenesis in autosomal-dominant polycystic kidney disease (ADPKD)

Proia D., Golemis E.

Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

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## Abstract

© 2018 FASEB. Autosomal-dominant polycystic kidney disease (ADPKD) is associated with progressive formation of renal cysts, kidney enlargement, hypertension, and typically end-stage renal disease. In ADPKD, inherited mutations disrupt function of the polycystins (encoded by PKD1 and PKD2), thus causing loss of a cyst-repressive signal emanating from the renal cilium. Genetic studies have suggested ciliary maintenance is essential for ADPKD pathogenesis. Heat shock protein 90 (HSP90) clients include multiple proteins linked to ciliary maintenance. We determined that ganetespiib, a clinical HSP90 inhibitor, inhibited proteasomal repression of NEK8 and the Aurora-A activator trichoplein, rapidly activating Aurora-A kinase and causing ciliary loss in vitro. Using conditional mouse models for ADPKD, we performed long-term (10 or 50 wk) dosing experiments that demonstrated HSP90 inhibition caused durable in vivo loss of cilia, controlled cystic growth, and ameliorated symptoms induced by loss of Pkd1 or Pkd2. Ganetespiib efficacy was not increased by combination with 2-deoxy-D-glucose, an glycolysis inhibitor showing some promise for ADPKD. These studies identify a new biologic activity for HSP90 and support a cilia-based mechanism for cyst repression.

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## Keywords

Cilia, Heat shock protein 90, PKD1, Polycystins, Renal cyst

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